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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/393,652	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,55 and 57-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54,55 and 57-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments, remarks, and substitute drawings, filed 1/29/07, are acknowledged.

2. Claim 56 has been cancelled.
Claims 72 and 73 have been added.
Claims 54, 55, and 57-73 are being acted upon.

3. The drawings filed 1/29/07 remain unacceptable and have not been entered.

Applicant has indicated in the instant Remarks the details of the changes to the Drawings. Again, it is noted that in a number of instances the substance of the Drawings has been changed. As set forth previously, the handwritten notes in the drawings have been removed, thus deleting information.

4. The previous rejection under 35 U.S.C. 102(b) has been withdrawn given the newly recited limitation comprising the administration of 100μg or more of HSP90-peptide complexes.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 54, 55, 57-71, and newly added Claims 72 and 73 stand/are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for inhibiting the rejection of BALB/cJ skin when transplanted onto a C57BL/6 mouse, said method comprising administering to a C57BL/6 mouse gp96 purified from a BALB/cJ source, said administration comprising subcutaneous injection of 100ug 10 days prior to transplantation, repeated 3 days prior to transplantation,

does not reasonably provide enablement for:

a method for inhibiting rejection of a grafted cell, tissue, or organ in a mammal comprising administering to a mammal a composition comprising a purified complex consisting

essentially of an HSP90 family heat shock protein or a gp96 heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cell, tissue, or organ, and wherein the composition is administered after/prior to the cell, tissue, or organ being grafted to the mammal.

As set forth previously, little is known regarding treating or preventing graft rejection by administering HSPs. Indeed, the Inventor himself has repeatedly taught that in numerous contexts, both *in vitro* and *in vivo*, all heat shock proteins are immunostimulatory (see for example, U.S. Patents No. 5,985,270, 5,750,119, and 5,961,979). Accordingly, claims based on the highly unexpected assertion that HSPs are sometimes immunosuppressive when administered in vivo, require enablement commensurate with the scope of the claims.

Regarding the scope of the claims, given the highly unexpected nature of the instant invention, said invention cannot be considered to be enabled for any HSP not demonstrated (in the specification or art) to be immunosuppressive in the instant context (graft rejection). It is noted that the specification discloses only the use of BALB/cJ mouse and unknown rat gp96, and only in the context of transplant into a C57BL/6 mouse. The results of Experiment 2 demonstrate that rat gp96 treatment worked little (if any) better than control (no) treatment in the instant method. Accordingly, not even all gp96's (even those likely to be closely related) can be considered to be enabled. The most likely conclusion to be drawn from the limited data is that the gp96 must derive from the same genetic source as the graft.

A review of the specification discloses that the maximum disclosed dosage range is "about 5ug to about 5000ug" of complex (page 31). There is no disclosure in the specification of any dosage greater than "about 5000ug" in any context. The specification also discloses that a 20-25g mouse is administered 100-200ug of complex; the specification also demonstrates that lesser dosages are ineffective (see Experiments 1 and 2). As a human is roughly 3000 times the size of a mouse, the appropriate dosage for a human would likely be 300,000-600,000ug of complex - at least 60 times higher than the highest dosage disclosed by the specification. As a horse or cow is roughly 10 times the size of a human, the maximum disclosed dosage would likely fall 600 times short of what would be required to be effective in said mammals (it is noted that the claims now recite a dosage of 100µg or more).

It is the Examiner's position then that given the broad scope of the claims and the limited working examples, the specification cannot be considered enabling for the invention as claimed.

Applicant has submitted WO 02/072133 as enablement for "HSP70 family members" in the method of the instant claims. Upon review said document cannot be considered enabling for the use of HSP70 family members in the method of the instant claims. The document discloses the use of BiP (a HSP70) only in a highly artificial arthritis model. Presumably, Applicant's argument is that artificial arthritis and graft rejection are both TH1- mediated, thus a treatment for the artificial arthritis model would be effective as a treatment for graft rejection. The document indicates that BiP has an immunosuppressive effect because it stimulates IL-10 release (page 8) which induces an anti-inflammatory shift towards TH2 (page 23). This capability of inducing IL-10 release and the subsequent shift towards TH2 is presumably how BiP might function in inhibiting graft rejection. There exists however, a significant body of work indicating that IL-10 is not

necessarily immunoprotective, a shift towards TH2 is not necessarily desirable, and a HSP70 might actually be a facilitator in numerous models of TH1-mediated pathology. See for example, Pakala et al. wherein it is taught that in a disease model thought to be TH1-mediated, induction of IL-10 and a TH2 response, rather than being protective or benign, was highly pathogenic. The work calls into question the entire concept of a shift towards TH2 as a treatment of TH1 pathologies. See also McFarland, wherein as early as 1996 it was taught the "Mechanisms of autoimmunity (and presumably graft rejection) are more complicated than a simple TH1-Th2 dichotomy". The reference further teaches additional instances wherein the TH2 response worsens diseases thought to be THI mediated. As regards an HSP70 family member specifically, Mycko et al. teaches the enhancement of another TH1 mediated disease by over-expression of HSP70 and increased Class II presentation of an autoantigen. The combined references indicate that, at best, the use of a HSP70 in a method of inhibiting a TH1-mediated response [including graft rejection] must be considered to be highly unpredictable.

In the specific context of allograft reaction, Pockley teaches that "the balance between protective and damaging effects [of HSPs] and the precise influence of these responses on graft outcome is unclear". In some instances HSPs appear to promote the development of acute and chronic graft rejection whereas in other instances heat shock proteins appear to be cytoprotective. The reference concludes that "The role of heat shock proteins in allograft immunity is unclear and more insight into the processes by which heat shock proteins encounter and are recognized by the recipient immune system after transplantation is required." Clearly then, the reference serves to define the invention of the instant claims as being unpredictable.

Applicant's arguments, filed 1/29/07, have been fully considered but they are not persuasive. Applicant argues that the specification fully enables the claimed method.

It is noted that Applicant admits, "Applicants do not dispute the surprising and unexpected nature of their discovery that heat shock proteins have immunosuppressive properties". Accordingly, it remains the Examiner's position that the enablement provided by the specification must be commensurate in scope with the breadth of the claimed invention. Given the limited nature of the two very similar disclosed experiments, it remains the Examiner's position that the enablement provided by the specification is insufficient given the breadth of the claims.

Applicant discounts the teachings of Pockley.

Pockley teaches what it teaches - that HSPs are unpredictable in the context of allograft rejection. Applicant's arguments that the biological activities of the endogenous HSPs of the reference might differ from the purified

HSP-peptide complexes of the instant claims is not supported by any evidence of record.

Applicant argues that the claimed immunosuppressive effects have been demonstrated in five different animal models.

Applicant is advised that the specification as filed must be enabling. The instant specification provides just a single animal model that fails to provide enablement commensurate in scope with the claimed method.

Applicant again cites the Inventor's post-filing work.

As set forth previously, regarding Chandawarkar et al. 2004, the discrepancies between the 1999 findings and conclusions and the 2004 findings and conclusions are attributed to differences in immunizing dosages of antigen. This is clearly an issue that was not understood at the time of filing of the instant application. As set forth in MPEP 2164.05, a specification *must* be enabled at the time of filing. Applicant cannot submit post-filing references in an attempt to enable that which was not enabled at the time of filing because it was not understood at the time of filing. Thus, neither Chandawarkar et al. 2004 nor Kovalchin et al. 2006 can enable the method of the instant claims. And note again the teachings of Pockley 2001, "the balance between protective and damaging effects [of HSPs] and the precise influence of these responses on graft outcome is unclear". What is clear, however, is that if the method of the instant claims was not enabled in 2001, it was not enabled when the application was filed in 1999. Further, none of Inventor's work of record demonstrates how findings in mouse models might be translated to the treatment of human graft rejection.

Applicant argues that the specification demonstrates the immunosuppressive effect of "high doses" of gp96-peptide complexes.

More precisely, the specification demonstrates a method for inhibiting the rejection of BALB/cJ skin when transplanted onto a C57BL/6 mouse, said method comprising administering to a C57BL/6 mouse gp96 purified from a BALB/cJ source, said administration comprising subcutaneous injection of 100 ug 10 days prior to transplantation, repeated 3 days prior to transplantation. This is not the broad method of the instant

claims.

Applicant reviews Experiment 2 of the specification. Applicant again cites Chandawarkar et al. 2004 and Kovalchin et al. 2006.

Applicant's review of Example 2 is noted. Applicant is again advised that the results of the 2004 and 2006 references are silent regarding enablement at the time of filing in 1999.

Applicant dismisses the negative results of Experiment 2 of the instant specification.

Applicant's dismissal of Applicant's own results is noted. However, absent positive results commensurate in scope with the claimed method, said method is still not enabled.

Applicant asserts that sequence homology among the HSP90s enables the use of any HSP90 in the claimed method.

Applicant's assertion is noted, however, mere assertion does not comprise enablement. Additionally, the art is replete with examples of proteins comprising just single amino acid differences wherein the proteins comprise different biological functions.

Applicant misrepresents the Examiner's position with the assertion that "The Examiner contended that the appropriate dose for a human would be in the range of 300,000 to 600,000 micrograms based on the teaching in the specification that an effective dose for a 20 to 25 gram mouse is 100 to 200 micrograms, since "a human is roughly 3000 times the size of a mouse.""

The Examiner's actual position, as set forth above, is "As a human is roughly 3000 times the size of a mouse, the appropriate dosage for a human would *likely* be 300,000-600,000ug of complex". The Examiner's premise is base on the lack of sufficient teachings in the specification in this regard. As set forth previously, the *entire* teaching of the specification regarding dosage comprises, "Similar high dosages of 100-200ug, or more than 200 ug, of hsp may also be effective in the treatment of larger mammals including humans".

Applicant cites U.S. Patent No. 6,017,540.

The Examiner finds the citing of the '540 patent, at best, curious, in light of Applicant's previous vigorous arguments that findings regarding the immunostimulatory nature of HSPs cannot be extended to predict the immunosuppressive nature of HSPs. Regardless, a review of the reference shows that *a dosage of 5-500ug of HSP90-antigen complex is immunostimulatory.* Clearly then, Applicant's own patent teaches that the claimed method of immunosuppression is not enabled.

Applicant cites the Inventor's arguments set forth in the interview of 1/16/07.

The Inventor's opinion is noted. However, there is no evidence of record in support of it.

Applicant cites several newly submitted references in support of the claimed method.

A review of the references shows that each of them teaches the *immunostimulatory* nature of HSPs. As Applicant previously argued that the immunostimulatory nature of HSPs reveals nothing regarding the immunosuppressive nature of HSPs, it is unclear why Applicant would cite these references at this time. It would appear that Applicant is attempting to pick and choose individual properties (i.e., dosing properties) in support of the claimed method, while ignoring the fact that in all cited contexts the HSPs are *immunostimulatory*. Such an argument is not persuasive.

Applicant argues, "The Examiner has not explained why the disclosure is insufficient".

Quite simply, the disclosure is insufficient because the prior art teaches that HSPs are immunostimulatory. Applicant does not dispute that the immunosuppressive nature of HSPs in some contexts is "surprising" and "unexpected". Further, given Applicant's own patent disclosing that a dose of 500ug of HSP90-antigen complex is immunostimulatory, the method of the instant claims comprising a method of administering a dose 100ug or more of HSP90-peptide complex for immunosuppression is not enabled.

Applicant argues that the determination of dosage is routine.

The Examiner disagrees in this instance. As set forth previously, the establishment of an effective dose of HSP for immunosuppression is not a matter of simply ramping up dosages until an effective dosage is determined. In this case, it has been well-documented that HSPs are more often than not *immunostimulatory*, thus, an improper dosage would as likely kill a patient in need of immunosuppression as benefit him. Also note that the Experiments of the instant specification comprise methods of trial-and-error wherein dosages are simply ramped up. Such methods could not be used on humans.

Applicant argues that "the Examiner is improperly requiring safety and efficacy data in humans for satisfaction of the enablement requirement of 35 U.S.C. § 112".

No such requirement has been made. An enabling specification is, however, required.

Applicant argues that the contradictory teachings of Chandawarkar et al. 1999 and Chandawarkar et al. 2004 are countered by the "plain language of the specification".

It remains the Examiner's position that the mere three sentences in the specification cited by Applicant cannot be considered to be sufficiently enabling of the claimed method.

Applicant argues that the post-filing references Chandawarkar et al. 2004 and Kovalchin et al. 2006 were submitted to "establish the truth of the statements in the specification".

It remains the Examiner's position that the references raise considerations not addressed in the specification. For this reason alone the references further demonstrate a lack of enablement at the time of filing. And as set forth previously, Applicant has ignored the discrepancies between Chandawarkar et al. 1999 and Chandawarkar et al. 2004. A review of Chandawarkar et al. 2004 as well as Chandawarkar et al. 1999 is enlightening. Chandawarkar et al. 1999 teaches that the source of the gp96 complex is indeed critical to its immunosuppressive properties, see Figure 3B, "Immunization with high doses (10 mg i.d.) of Meth A gp96 but not liver gp96 elicits concomitant immunity to Meth A sarcoma", i.e., liver gp96 was not immunosuppressive in a Meth A tumor graft context. Thus, at the time of filing, the method of the instant claims was clearly not enabled in its

breadth. Chandawarkar et al. 2004 teaches that the results of the 1999 work were due to "differences in experimental design" and "interpretation". The newer work teaches that it was later discovered that an immunizing dose (in this case Meth A, or in the context of the method of the instant claims, the cell, tissue or organ graft antigens for which inhibition against rejection is desired) *must* be administered before the suppressive high dose of gp96 is administered (page 617, column 1). This is clearly not a consideration addressed by the instant specification. It would seem then that the Inventor's own work demonstrates that immunosuppression employing hsps, in the context of the inhibition of graft rejection, comprises a much more complex issue than is disclosed in the instant specification, requiring consideration of numerous issues that are not disclosed in the specification. Accordingly, the specification cannot be considered to be enabling of the method of the instant claims.

Additionally note that just a single "high dose" (100ug of HSP90-peptide complex) was used in all of the examples. Said single dosage in a single animal species (mouse) is not representative nor commensurate in scope with the range of dosages for use in any species encompassed by the claims.

Applicant cites page 37 of the specification in support of the claimed limitation of administering the HSP90-peptide complex before engraftment.

A review of the page shows that only the generic concept of pretreatment was considered at the time of filing. Page 37 reveals no data, no discussion of timing, indeed there is no specific teaching at all at the cite.

7. Claims 54, 55, 57-71, and newly added Claims 72 and 73 stand/are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) The method of Claim 54 … effective to inhibit graft rejection … wherein the composition is administered after the grafted cell, tissue or organ.

B) The method of Claim 55 … effective to inhibit graft rejection … wherein the composition is administered prior to the grafted cell, tissue or organ.

C) The method of Claim 56 … comprising administration of 100ug or more of the hsp complexes [**NOTE**: this limitation is now recited in Claims 54 and 55 and Claim 56 has been canceled].

Regarding A) Applicant indicates that support for the new limitations can be found at pages 11 and 31, and at pages 4 and 36 of the specification. A review of pages 11 and 31 shows support only for a method of treating or preventing graft rejection or eliciting immune tolerance wherein the composition is administered after the grafted cell, tissue or organ. At pages 4 and 36 the specification teaches only the administration of hsps, and not compositions comprising purified complexes of the claims.

Regarding B) Applicant indicates that support for the new limitations can be found at pages 11 and 31, and at pages 4, 37, and 38 of the specification. A review of pages 4, 37, and 38 shows support only for a method administering donor tissue prior to the administration of hsps, i.e., no administration of cells or organs, and no administration of the purified complexes of the claim.

Regarding C) Applicant indicates that support for the new limitations can be found at pages 11 and 31, and at pages 4, 37, and 38 of the specification. The specification does not disclose administration of 100ug or more of complexes. Note that original Claim 17 comprised the dosage limitation of current Claim 56 but the method was not the method of the instant claim.

Applicant's arguments, filed 1/29/07, have been fully considered but they are not persuasive.

Regarding A), Applicant now cites page 10, 12, 33, 36, 38, and 39, in addition to page 11. Applicant asserts that inhibiting is merely a "clarification" of treating or preventing.

It is unclear why the terms treating or preventing would require "clarification"; both are well-known in the art. Regardless, inhibiting comprises a different scope than does treatment or preventing as treatment need not necessarily include inhibiting and inhibiting need not encompass prevention. Regarding the cites at pages 36, 38, and 39, the specific examples provide insufficient support for the broad claims. While the term inhibiting is recited at page 36, it is recited only in the context of "the use of hsp gp96 in immunoprophylaxis in experimental skin graft rejection in mice".

Regarding B), Applicant argues that the claim actually recites the administration of cells obtained from donor cells tissue or organ.

The second to last line of the claim recites "... administered prior to the cells tissue, or organ being grafted ...".

Applicant argues that "small portions" of tissue constitute cells.

It is the Examiner's position that the terms "a small portion of tissue" and "cells" are not synonymous.

Regarding C), Applicant now cites page 32 of the specification.

The cite at page 32 encompasses a dosage of HSP-peptide complex for the prevention of graft rejection and then only in the context of a dosage for "larger mammals, including humans". This combination of limitations is not found in the claims.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

11. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application

Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

4/24/07

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600